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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HL

Office Action Summary	Application No.	Applicant(s)	
	10/056,788	ALLEN, JAMES	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9,11-14,16-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/3/05 has been entered.

Claims 1-9, 11-14, and 16-21 are pending.

Applicant's traversal, the amendment to claims 1, 3, 11, 12, and 16 in the paper filed on 1/3/05 is acknowledged and considered.

Election/Restrictions

Claims 5 and 6 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/27/03.

Claim Objections

Claims 12-14 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 12-14 are broader than the claim (claim 3) from which they depend. Claims 12-14 recite delivering said preparation to a vascular conduit of said

mammalian subject and claim 3 recites delivering said preparation to at least one muscle cell. While it is noted that a vascular conduit can be found in a muscle cell, it is also noted that vascular conduit can also be found in other types of cells that are not muscle cells, e.g., epithelial cells.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-9, 11-14, and 16-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The removal of the limitation 'therapeutic effect' in claims 1, 3, and 16 and claims dependent therefrom (claims 2, 4, 7-9, 11-14, 17-21) resulting in broadening of the claimed methods to encompass a general method of delivering a heterologous nucleic acid or expressing a protein in a mammalian subject is not supported by the as-filed specification. Applicant has not pointed out where the amended claims are supported, nor does there appear to be a written description of the claim a general method of delivering and/or expressing a protein encoded by a heterologous nucleic acid in the application as filed. See MPEP § 2163.06. The examiner has reviewed the application and cannot find support for the amended claims.

Claims 1-4, 7-9, 11-14 and 16-21 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing Factor IX in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid (HNA) encoding a factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal, does not reasonably provide enablement for a method of delivering a heterologous nucleic acid to a mammal comprising administering at least one rAAV virion comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to expression control elements to at least one muscle cell using a genus of administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to a gene transfer method using a rAAV virion comprising an AAV-6 capsid and a heterologous nucleic acid (HNA) operably linked to a promoter. The applicant contemplates using the method to treat a variety of diseases. See pages 11-14 of the instant specification. Therefore, the breadth of the claims is considered broad.

In view of the specification, the only asserted use for delivering a heterologous nucleic acid or expressing a protein encoded by a heterologous nucleic acid to at least one muscle cell in a mammal using rAAV virion comprising an AAV-6 capsid and a heterologous nucleic acid is for treating a disease. In addition, the working examples in the specification are directed to

delivering and expressing a protein (Factor IX protein) encoded by a heterologous nucleic acid to a mammalian subject for treatment of a disease, e.g., hemophilia (expressing said protein at a therapeutic level in said mammal). See pages 11-14 of the instant specification. Thus, these claims will therefore be evaluated based upon gene therapy use.

Furthermore, and with respect to claims directed to any gene therapy directed to any treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed, gene therapy was considered unpredictable.

The applicant contemplates using rAAV-6 virion comprising a heterologous nucleic acid (HNA) to treat a variety of disorders and/or diseases in a mammal by delivery of rAAV comprising an AAV-6 capsid to muscle cells by intramuscular (i.m.) injection or by administration into the bloodstream of the mammal (see pages 10-12). The applicant teaches production of a recombinant AAV-6 factor IX virion (Example 1, pages 16-19). The applicant teaches i.m. administration of said virion to RAG-1 female immunodeficient mice (pages 19-20). The specification teaches treating hemophilia B dogs having hemophilia B using i.m. injection with said virion (Example 3, pages 20-21). The specification contemplates hemophilia B treatment in humans with AAV6-human factor IX (page 21).

The specification provides sufficient guidance and/or factual evidence for expressing a Factor IX protein in a mammal by i.m. administration of rAAV virion comprising an AAV-6

capsid to muscle cells comprising a HNA encoding a factor IX protein operably linked to expression control elements. However, in view of the breadth of the claims, the specification as filed does not provide sufficient guidance and/or factual evidence for one skilled in the art to use the full scope of the claimed invention because claims 3, 4, 7, 11-14, and 16-21 read on treating a variety of diseases (see pages 10-12) in a mammalian subject using said rAAV virion. In addition, claims 1-4, 7-9, 11-14, 16, and 19-22 encompass using any route of delivery for providing said rAAV virion to muscle cells in vivo or administering said rAAV virion to a subject using any route of administration (e.g., artery or vein).

The claimed method encompasses using rAAV virions comprising a HNA for treating a genus of diseases. The specification does not provide sufficient guidance and/or factual evidence for practicing the full scope of the claimed invention. The art of record teaches several problems with gene therapy (See Rubanyi, Molecular Aspects of Medicine, Vol. 22, 2001, pages 113-142, Orkin et al., "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy" December 7, 1995, Anderson, *supra* and Verma, *supra*). While, it is acknowledged that certain types of gene therapies have been cited in the art as treating a particular disease or genetic disorder using distinct material and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation. The art of record further teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the gene therapy method embraced by the claimed invention (See Verma, Anderson, and Rubanyi).

In addition, claims 1-4, 7-9, 11-14, 16, and 19-22 encompass using any route of delivery for providing said rAAV virion to muscle cells in vivo or to a subject. The applicant teaches using intramuscular (i.m.) administration for targeting muscle cells. However, the claims read on using all routes of delivery to target muscle cells. With respect to targeting muscle cells, the art of record and the specification do not teach how to use all routes of administration to target muscle cells other than direct administration (e.g., i.m.). Monahan teaches rAAV are able to transduce a wide range of tissue types leading to gene expression in several types of cells (Molecular Medicine Today, Vol. 6, pages 433-440, 2000). Since rAAV can transduce several different types of cells in a mammal, the specification does not teach one skilled in the art how to sufficiently target enough rAAV to muscle cells using any route of administration other than direct administration to a muscle cell to produce gene expression at a therapeutic level.

With respect to claims 16 and 19-21, the claims read on using a genus of administration routes to delivery the AAV comprising an AAV-6 capsid and comprising HNA to a mammal, the applicant teaches how to use direct administration to deliver Factor IX to the muscle of a mammal. However, the claims read on using a genus of administration routes (e.g., vein, artery, muscle, oral, rectal, etc.) to deliver and/or express at least one HNA in a mammal. See page 12 of the instant specification. The art of record teaches delivering and expressing Factor IX in a mammal using an AAV vector, wherein the AAV is selected from AAV1 to AAV6 (US Patent 6,093,392). The prior art further teaches delivering to a mammal via portal vein or hepatic artery rAAV virions comprising a nucleotide encoding Factor VIII (US 6,221,349 cited on an IDS). In view of the prior art and the guidance provided in the specification, one skilled in the art would have been able to practice delivering rAAV comprising an AAV-6 capsid and a HNA encoding

Factor IX using the administration routes taught in the prior art. However, the claims are broader than what is taught in the prior art and the specification. For example, as stated above, the claims read on using rAAV virions comprising a HNA for treating a genus of diseases. There is no guidance in the specification or the prior art for correlating the results in the working examples taught by the applicant in the instant specification to using the claimed method to treat a genus of diseases.

In addition, treating each disease embraced by the claimed method would require a certain amount of gene expression and/or regulation in a particular organ or tissue of the mammal. For example, several lysosomal disorders result from lack of expression of an enzyme in tissues including the brain (e.g., Fabry disease). The specification does not teach one skilled in the art how to express the HNA at a therapeutic effect in the brain of a mammal with the lysosomal disorder by delivering and/or expressing the HNA in at least one muscle cell of the mammal. The specification does not provide sufficient guidance for how to reasonably extrapolate from using i.m. injection of AAV6 virion comprising a HNA encoding Factor IX to a method of treating all diseases using a genus of administration routes to provide a therapeutic effect in cells for all diseases.

In addition, with respect to using AAV comprising an AAV-6 capsid to treat any disease contemplated by the specification, it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of gene therapy, for those skilled in the art to experiment with any delivery route and/or level of HNA expression so as to provide a therapeutic effect for any disease as intended by the as-filed specification at the time the invention was made.

See also Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification for treating a particular disease using the claimed method; the specification does not provide reasonable detail for what protocols are required for different methods of gene therapy, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed methods.

In addition, the art of record teaches problems with using rAAV in gene therapy (Monahan, *supra* and Hortelano et al., Art. Cells, Blood, Subs., and Immod. Biotech. Vol. 28,

pages 1-24, 2000, and Wang et al., PNAS, Vol. 97, pages 13714-13719, 2000). The genome of AAV is only 4.7kb-5.0kb, which is too short to use for delivering some nucleic acid sequences, e.g., full-size of hFVIII cDNA, CFTR, and the dystrophin gene. Hortelano teaches, "Despite the promising results obtained with AAV vectors delivering FIX, it has not yet been used to deliver FVIII (page 10)." Wang teaches, "AAV are too small (5kb) to package the 14-kb dystrophin cDNA (page 13714)." The specification does not teach one skilled in the art how to overcome the size limitation of AAV vectors. The specification does not provide sufficient guidance and/or factual evidence to the art for one skilled in the art to overcome the problems with AAV size limitation and make a genus of rAAV virions comprising a HNA.

Thus, it would take one skilled in the art an undue amount of experimentation to practice the full breadth of the claimed invention. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed methods generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the prior art, at the time the invention, was made only provide sufficient guidance and/or evidence to reasonably enable the for a method of expressing Factor IX protein in at least one muscle cell of a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements, wherein the rAAV is directly administered to at least one muscle cell in the mammal and not for

the full scope of the claimed methods. Given that gene therapy wherein any rAAV is employed to treat a disease or a medical condition in a mammalian subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any rAAV virion cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the full breadth of the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 1/3/05 have been fully considered but they are not persuasive.

Applicant argues that "only an enabling disclosure is required, applicant need not describe all actual embodiments" and "even in unpredictable arts, a disclosure of every operably species is not required" (MPEP 2164.02, 2164.03) and MPEP 2164.08.

Applicant's argument is acknowledged and is not found persuasive. While it is acknowledged that applicant need not describe all actual embodiments to enable a genus, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. See In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). As stated above, in the enablement rejection, the claims are broad. The methods contemplated by the applicant in the specification are directed different methods. The subject matter embraced by the claims encompass treating a variety of diseases and/or disorders that require different method steps, e.g., targeting the HNA to different cells; expressing the HNA in a target tissue or an organ; expression and/or regulation of the HNA used to treat a disease and/or disorder. In view of the In Re Wands Factors, one skilled in the art could not make and use the entire scope of the claimed invention without undue experimentation.

Furthermore, the argument that applicant may claim more broadly than his preferred embodiment (MPEP 2164.08) is not found persuasive because the rejection is not based on the claims not reciting a critical feature, the rejection was based on the In Re Wands Factors and that it would take one skilled in the art an undue amount of experimentation to practice the claimed invention.

Applicant argues that Applicant has amended claims to no longer require treatment of any specific disease or expression of a heterologous nucleic acid to provide a therapeutic effect. The specification discloses that methods of the instant invention may be used for other reasons than treating a disease. See pages 14-15 of the instant specification.

Applicant's argument is not found persuasive because the claims are broader than the uses contemplated by the specification on pages 14-15. Other than the therapeutic use contemplated in the specification, the as-filed specification does not provide any guidance or factual evidence for other uses of the claimed method that would meet the requirements of 35 U.S.C. 101. The specification supports the examiner's interpretation of the only intended use of the claimed methods. See pages 11-14 of the instant specification. In addition, other than the assertion that the method can be used for reasons other than treating a disease, the applicants provide no guidance and/or evidence to support these assertions. Therefore, applicants' assertions regarding using the instant invention for other reasons than treating a disease is not compelling. See In re Scarbrough, 500 F.2d 560, 565, 182 USPQ 298, 301-02 (CCPA 1974) and MPEP § 716.01(c), which recites that attorney's arguments, cannot take the place of evidence.

Applicant argues that level of skill in the art of molecular biology is high and one of skill in the art would know of public databases that contain sequences for a number of disease-related

genes. One of skill in the art could use the list of genes to deliver and expressed using the methods and rAAV-6 vectors of the present invention.

Applicant's argument is not found persuasive because the rejection is not based on whether known sequences could be used for treating a disease embrace by the claimed method. The rejection was based on In Re Wands Factors and that it would require undue experimentation for one skilled in the art to use the claimed method to treat a genus of diseases and/or disorders.

Applicant argues that with respect to the office action asserting that the art of record teaches problems with using rAAV in gene therapy by listing 3 proteins whose full-length genes are too long to be packaged in a rAAV virion, applicants are not required to show enablement of every species. As pointed out in applicant's 5/6/04 response, as of the filing date one of the listed genes (Factor VIII) has already been delivering using rAAV vector, albeit not the full-length gene. In addition, a number of other genes have in fact been delivered and expressed using rAAV vectors despite the known vector size limitation.

Applicant's argument is not found persuasive because the specification as filed and the prior art, at the time the application, was filed do not provide sufficient guidance to use rAAV virions comprising an AAV-6 capsid because the specification and the state of the art are absent of how to overcome the problem of making rAAV virions comprising an AAV-6 capsid whose full length genes are too big to be packaged in the virions. The AAV vector taught in the prior art was directed to AAV-2 vectors and did not teach one skilled in the art to make and use a rAAV virion comprising an AAV-6 capsid. In addition, the post-filing articles (Tsai 2003; Galeano, 2003 and Mochizuki, 2004) cited in the argument indicate that the specification as filed

did not teach one skilled in the art how to make and use rAAV virions comprising an AAV-6 capsid comprising a gene that are too big to packaged in the rAAV virions. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997). In addition, the post-filing arts indicates that there are method steps required to practice the claimed invention that are missing from the specification as-filed.

Applicant argues that using any route of administration in the claimed method is within the skill in the art (paragraph 0035 of the instant application) and paragraph 0034 of the instant application discloses the use of isolated limb perfusion for delivery of rAAV-6 virions to a mammalian subject.

Applicant's argument is not found persuasive for the reason of record. Furthermore, other than the assertion that using any route of administration in the claimed method is within the skill in the art, the applicant provides no guidance and/or evidence to support this assertion. Therefore, applicant's assertion regarding the unpredictability of using a genus of administration routes in the claimed methods is not compelling. See MPEP § 716.01(c). In addition, US patent 6,177,403 cited in the specification is directed to direct administration to extravascular tissue of an animal and does not disclose how to delivery rAAV-6 virions to mammalian subject using a genus of administrations routes.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
(f) he did not himself invent the subject matter sought to be patented.

Claims 1-4, 7-9, 11, and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by High et al., (IDS, US Patent 6,093,392).

High anticipates claims 1, 3, 4, 7, 8, 11, 16, 17, and 18 because High teaches administering rAAV comprising a nucleic acid encoding Factor IX (which is a secreted protein) operably linked to an expression control element to a muscle tissue of a mammal (columns 26-30). Administering rAAV as taught by High would anticipate delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in solution (column 20). High teaches that any suitable AAV vector can be used in the method, including AAV1, AAV3, AAV4, and AAV6 (column 11, lines 52-57). Furthermore, High teaches targeting the skeletal muscle with the AAV vector (columns 25-26).

In addition, the limitation "providing a preparation of rAAV virions lacking the components to form replication competent adenovirus" in the claims would read on any preparation of AAV vectors because the claims read on an AAV virion lacking components necessary to form replication competent adenovirus and AAV vectors do not have components necessary to form replication competent adenovirus.

High anticipates claims 2 and 9 because High teaches that Factor IX can be human Factor IX (columns 26-29).

Applicant's arguments filed 1/3/05 have been fully considered but they are not persuasive because the limitation "providing a preparation of recombinant rAAV virions lacking the components necessary to form replication competent adenovirus" in the instant claims could read on either a preparation of rAAV virions lacking the components necessary to form replication competent adenovirus or rAAV virions lacking the components necessary to form replication competent adenovirus. Thus, when the claim is read with rAAV virions lacking the components necessary to form replication competent adenovirus, High anticipates the claims.

Amending the limitation in the claim to indicate that the preparation and not the rAAV virions lack the components necessary to form replication competent adenovirus would overcome the rejection as being anticipated by High.

Claims 3, 4, 7, and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Miller et al., (US 2004/0248288).

The applied reference has a common inventor (James Allen) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Miller anticipates claims 3, 4, 7 and 16 because Miller teaches delivering an AAV comprising a gene encoding human placental alkaline phosphatase (secreted protein) operably linked to a promoter to airway epithelial cells, wherein the AAV comprises capsid protein of AAV-6 (page 14). Miller teaches the delivery of the AAV to airway epithelial cells in a mouse resulting in the delivery of the AAV to muscle cells in the mouse and expression of the gene in the muscle cells (pages 9 and 10, Figs 4 and 5). Administering rAAV as taught by Miller would anticipate delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in solution (page 10).

In addition, the limitation "providing a preparation of rAAV virions lacking the components to form replication competent adenovirus" in the claims would be anticipated by Miller because Miller teaches using a single adenovirus helper protein E4orf6 to produce helper-free AAV vectors (page 11). This would read on the limitation because the claims read on an AAV virion preparation lacking components necessary to form replication competent adenovirus and Miller teaches producing adenovirus free AAV.

Claims 3, 4, 7, and 16 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Claims 37 and 38 from U.S. application 10/169,785 recite delivering an AAV comprising a gene operably linked to a promoter to airway epithelial cells, wherein the AAV comprises capsid protein of AAV-6. The claims from '785 do not specifically recite expressing the gene encoding a secreted protein in at least one muscle cell. In addition, the claims from '785 do not

specifically recite providing a preparation of rAAV lacking the components necessary to form replication competent adenovirus.

However, when claims 37 and 38 are read in light of the specification, the claims from '785 read on instant claims 3, 4, 7, and 16 because the specification teaches that delivering AAV comprising an AAV-6 capsid and comprising a promoter operably linked to human placental alkaline phosphatase (a secreted protein) to airway epithelial cells of a mouse results in delivery of the AAV to muscle cells and expressing of the gene in the muscle cells (pages 22-26, Figs 4 and 5). The specification further teaches using a single adenovirus helper protein E4orf6 to produce helper-free AAV vectors, which would read on a preparation of rAAV lacking the components necessary to form replication competent adenovirus (pages 22-30).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, and 16-21 read on expressing a heterologous nucleic acid encoding a protein (e.g., Factor IX protein) in a mammal comprising providing a preparation of rAAV virions, wherein the preparation lacks the components necessary to form replication competent adenovirus, and administering to said mammal recombinant adeno-associated virus (rAAV) virions comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to a promoter. The claims do not require expressing the protein at a therapeutic level.

Claims 3, 4, 7-9, and 11-14 read on delivering a heterologous nucleic acid encoding a protein to at least muscle cell of a mammal comprising providing a preparation of rAAV virions, wherein the preparation lacks the components necessary to form replication competent adenovirus, and administering to said mammal recombinant adeno-associated virus (rAAV) virions comprising an AAV-6 capsid and a heterologous nucleic acid operably linked to a promoter. Thus, these claims only require delivering the heterologous nucleic acid to at least one muscle cell of a mammal.

Claims 3, 4, and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al., (US Patent 6,156,303) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

Russell teaches delivering to a mammal an AAV6 viral particle comprising a nucleic acid sequence encoding a protein, operably linked to a promoter and expressing the protein in the mammal (abstract, columns 2-3, 16-17, 26, and 72). Russell further teaches delivering AAV6 viral particles to muscle cells (column 27, lines 1-15 and column 72). Russell teaches that the

AAV can be introduced locally by direct injection (column 26). Administering rAAV as taught by Russell would read on delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in a solution. However, Russell does not specifically teach using recombinant adeno-associated virus virions (rAAV) comprising an AAV-6 capsid, wherein said rAAV virion preparation is free of helper virus (e.g., adenovirus) in the method.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without adenovirus (pages 938-945). Matsushita teaches that elimination of adenovirus from the AAV vector production protocol results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Russell taken with Matsushita to make and use rAAV-6 virions, free of adenovirus, in an in vivo gene transfer method to muscle cells. One of ordinary skill in the art would have been motivated to make and use rAAV-6 virions, free of adenovirus, because Matsushita teaches that adenovirus free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/3/05 have been fully considered but they are not persuasive.

With respect to applicant's argument that Russell teaches away from the use of AAV-6 because Fig 5 indicates that AAV-6 vectors give lower levels of expression of AP than AAV-2 vectors in all six cells examined, the argument is not found persuasive because claims 3 and 4 do not require expression of the heterologous nucleic acid and the claims from '303 recite delivering an AAV viral vector to a muscle cell wherein the viral vector comprises an AAV6 vector genome, wherein the vector comprises a heterologous nucleic acid sequence, which would indicates that Russell is not teaching away from the use of AAV-6 for delivering a heterologous nucleic acid sequence to a mammalian cell.

In addition, claims 3 and 4 only require that the heterologous nucleic acid be delivered to at least one muscle cell of said mammal. While, it is noted that the features upon which applicant relies (i.e., expressing a protein in a mammal) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1-4, 7-9, 11, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over High et al., (IDS, US Patent 6,093,392) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

High teaches administering rAAV comprising a nucleic acid encoding Factor IX (which is a secreted protein) operably linked to an expression control element to a muscle tissue of a mammal (columns 26-30). High teaches that Factor IX can be human Factor IX (columns 26-29). High teaches that any suitable AAV vector can be used in the method, including AAV1,

AAV3, AAV4, and AAV6 (column 11, lines 52-57). Administering rAAV as taught by High would read on delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in solution (column 20). Furthermore, High teaches targeting the skeletal muscle with the AAV vector (columns 25-26). However, High does not specifically teach using recombinant adeno-associated virus 6 virions (rAAV-6), wherein said preparation of rAAV-6 virions is free of adenovirus.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without helper virus, e.g., adenovirus (pages 938-945). Matsushita teaches that elimination of adenovirus from the AAV vector production protocol results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of High taken with Matsushita to make and use a preparation of rAAV virions, free of adenovirus in an in vivo gene transfer method. One of ordinary skill in the art would have been motivated to make and use rAAV virions comprising an AAV-6 capsid, free of adenovirus, because adenovirus free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/3/05 have been fully considered but they are not persuasive.

Applicant argues that the unexpectedly high level of hF.IX expression achieved using the methods of the instant invention prove that the claimed invention is not obvious in light of High et al.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., rAAV-6 delivery showing circulating plasma concentration of human factor IX of 185 ng/ml and 190 ng/ml Factor IX in mouse at three to seven post injection using a dose of 2x1011 vg/kg) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 3, 12-14, 16, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over either High et al., (IDS, US Patent 6,093,392) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945) as applied to claims 1-4, 7-9, 11, and 16-18 above or Russell et al., (US Patent 6,156,303) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945) as applied to claims 3 and 4 and 16-17 above, and further in view of Couto et al (US 6,221,349, IDS).

Neither High taken Matsushita nor Russell taken with Matsushita specifically teach delivering and/or expressing a heterologous nucleic acid in a mammal comprising administering rAAV virions, lacking the components necessary to from replication competent adenovirus, comprising an AAV-6 capsid to a vascular conduit in the mammal, wherein the vascular conduit selected from either a vein or an artery.

However, at the time the invention was made, Couto teaches a method of delivering and expressing a coagulation protein encoded by a polynucleotide to a mammal comprising administering via portal vein or hepatic artery rAAV virions (Columns 49-51). Accordingly, in view of the prior art represented by Couto, one of ordinary skill in the art would have had sufficient motivation to deliver and express a coagulation protein via hepatic artery or portal vein with a reasonable expectation of success.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either High or Russell taken with Matsushita in further view of Couto to use a rAAV virions comprising an AAV-6 capsid in a gene transfer methods, wherein the rAAV virions are administered to either a vein or an artery of a mammal. One of ordinary skill in the art would have been motivated to deliver the rAAV to either the vein or artery of the mammal because Couto teaches that both delivery routes will result in expression of a protein encoded by a nucleic acid.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3, 4, 7, and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37 and 38 of copending Application No. 10/169,785.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 3, 4, 7 and 16 and the claims from '785 when read in light of the specification are obvious variants of one another.

Instant Claims 3 and 4 are directed to delivering a heterologous nucleic acid to at least one muscle cell in a mammal comprising providing a preparation of rAAV virions, wherein the preparation lacks the components necessary to form replication competent adenovirus, and administering rAAV virions to said muscle cell, wherein the rAAV virions comprising a heterologous nucleic acid encoding a protein. The limitation for Instant claim 7 is that the protein is a secreted protein. Instant Claim 16 is directed to expressing a heterologous nucleic acid in a mammal comprising administering rAAV virions, wherein the rAAV virions comprising a heterologous nucleic acid encoding a protein.

Claims 37 and 38 from '785 are directed to delivering an AAV comprising a gene operably linked to a promoter to airway epithelial cells, wherein the AAV comprises capsid protein of AAV-6. The claims from '785 do not specifically recite expressing the gene in at least one muscle cell.

However, when reading the claims in light of the specification, the claims are obvious variants of the instant claims 3, 4, and 7 because the specification teaches that delivering AAV comprising a promoter operably linked to human placental alkaline phosphatase to epithelial cells in a mouse results in delivery of the AAV to muscle cells and expression of the gene in said muscle cells (pages 22-26 and Figs 4 and 5). In addition, human placental alkaline phosphatase is a secreted protein. Miller teaches using a single adenovirus helper protein E4orf6 to produce AAV vectors, e.g., helper-free AAV vector (pages 24-30). See MPEP 804, which recites that the specification can always be used as a dictionary to learn the meaning of a term in the patent claim.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

This is a provisional obviousness-type double patenting rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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